Complete Summary

GUIDELINE TITLE

Use of gemcitabine in the treatment of advanced pancreatic adenocarcinoma.

BIBLIOGRAPHIC SOURCE(S)

Germond C, Maroun J, Moore M, Zwaal C, Wong S, Gastrointestinal Cancer Disease Site Group. Use of gemcitabine in the treatment of advanced pancreatic adenocarcinoma. Toronto (ON): Cancer Care Ontario (CCO); 2005 Jun 24. 21 p. (Practice guideline report; no. 2-10). [27 references]

GUIDELINE STATUS

This is the current release of the guideline.

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COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Advanced or unresectable pancreatic adenocarcinoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Gastroenterology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations about the use of gemcitabine for patients with unresectable or advanced pancreatic adenocarcinoma

TARGET POPULATION

Adults with unresectable or advanced pancreatic adenocarcinoma

INTERVENTIONS AND PRACTICES CONSIDERED

Gemcitabine

MAJOR OUTCOMES CONSIDERED

Primary Outcomes

Clinical benefit response, a composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight (see Appendix 1 of the original guideline document)

Secondary Outcomes

- Median survival
- One-year survival
- Median progressive-free survival
- Tumour response rate
- Symptomatic response
- Time to progressive disease

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

1998 Guideline

MEDLINE (1987 to May 1998), CANCERLIT (1988 to May 1998) and the Cochrane Library (1997, Issue 4) were searched using the following terms: "gemcitabine" (text word) and "pancreas" or "pancreatic neoplasms" (subject headings). CARL's UnCover database was searched for articles which had not yet been indexed in MEDLINE using the keywords "gemcitabine" and "pancreatic". The Physician Data Query (PDQ) database was searched to find ongoing trials (both those that are active and those that have recently closed). Recently published journals were searched manually.

2005 Update

The original literature search was updated using MEDLINE (through February week 4, 2005), EMBASE (May week 4, 2003 through week 10, 2005), CANCERLIT (through September 2002), the Cochrane Library (Issue 1, 2005), and the 1999 - 2004 proceedings of the annual meeting of the American Society of Clinical Oncology. The 2005 ASCO Gastrointestinal Cancers Symposium was also searched for relevant abstract reports. The National Cancer Institute (NCI) database (http://www.nci.nih.gov/search/clinical_trials/) was searched for ongoing trials on February 7, 2005. The updated literature searches from 2002 on were limited to randomized trials only.

Inclusion Criteria

Articles were selected for inclusion if they met the following criteria:

- Fully published articles or abstracts of gemcitabine treatment in patients with pancreatic cancer
- Phase I, phase II, and phase III trials were considered in this report.

2005 Update

After the first update in 2002, a decision was made by the Gastrointestinal Cancer Disease Site Group (DSG) that only Phase III randomized controlled trial reports of gemcitabine treatment in patients with pancreatic cancer would meet the inclusion criteria for review.

Exclusion Criteria

Papers published in a language other than English were not considered.

NUMBER OF SOURCE DOCUMENTS

1998 Guideline

Two phase I trials, one trial with both a phase I and phase II design, six phase II trials, and one randomized controlled trial (RCT) were initially reviewed.

2005 Update

Fifteen new randomized controlled trials were obtained during updating.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

1998 Guideline

As overall survival was reported for only one randomized controlled trial (RCT) and one phase II trial, no pooled estimate for survival across studies was calculated. Partial response rates were pooled across phase II trials to obtain a more precise estimate of the effect of gemcitabine. The pooled partial response rate provides an estimate of the activity of gemcitabine and should not be interpreted as a surrogate measure for overall survival or quality of life. The data were pooled by summing the number of partial responses across phase II trials and dividing this number by the total number of patients included in all phase II trials. The result was converted to a percentage and the 95% confidence intervals (CI) were calculated.

2005 Update

Updating activities obtained 15 new RCTs allowing for pooling of data. Overall survival at one-year was pooled using the Review Manager 4.2.1 meta-analysis software program (version date: April 9, 2003; © The Cochrane Collaboration). The random effects model was used for all comparisons, and results were expressed as relative risk ratios with a 95% confidence interval and p-value.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

1998 Guideline

The Gastrointestinal Cancer Disease Site Group (DSG) discussion centred around the one available randomized controlled trial. The DSG was concerned that the methodology used to assess clinical benefit had not been independently validated. Group members also felt that the potential for bias existed because trial physicians were aware of the treatment that patients received. The possibility that 5-fluorouracil (FU) may have worsened outcome compared to no treatment could have been addressed by having a no-treatment control arm, although a worsened outcome was considered unlikely. The DSG generally agreed that the study was clinically sound and that gemcitabine appears to be useful in the treatment of advanced pancreatic cancer, possibly benefiting asymptomatic patients by prolonging progression-free survival. The DSG was aware of the limitations of the data because only one trial has been published but thought that the final design was generally sound and that this trial remains the best available evidence to date for a patient population for which no other effective treatment exists. The emerging literature on this topic will be followed closely.

2005 Update

Adding known cytotoxic agents to gemcitabine has not yet resulted in a detectable one-year survival benefit, and carries the disadvantage of added toxicity. The study by Berlin et al suggests some improvement with the addition of 5-fluorouracil (p=ns), as does the study by Moore et al, which suggests an improvement with the addition of erlotinib (p=ns); therefore trials comparing gemcitabine monotherapy against a combination treatment also containing gemcitabine should be further explored in future randomized controlled trials (RCTs). The emerging literature on this topic will be followed closely.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner Feedback

Based on the evidence described in the original report and the draft recommendations presented in the original guideline document, feedback was sought from Ontario clinicians.

Practitioner feedback was obtained through a mailed survey of 63 practitioners in Ontario. The survey consisted of items evaluating the methods, results, and

interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Gastrointestinal Cancer Disease Site Group.

The final recommendations were approved by the Gastrointestinal Cancer Disease Site Group and the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Gemcitabine should be offered as treatment to patients with advanced or unresectable pancreatic cancer. There is evidence from one randomized controlled trial that gemcitabine improves symptoms and modestly improves survival in patients with advanced or unresectable pancreatic cancer. These patients were symptomatic, had a life expectancy of at least twelve weeks, and a Karnofsky performance status of at least 50% (equivalent to an Eastern Cooperative Oncology Group [ECOG] performance status of less than 3).

CLINICAL ALGORITHM(S)

A clinical algorithm is provided for assessment of clinical benefit.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- A total of 16 randomized controlled trials (RCTs) were obtained for this review. Three RCTs compared gemcitabine with other single-agents, and to date, only the trial by Burris et al (comparing gemcitabine with 5-fluorouracil [5-FU]) has detected a statistically significant difference favouring gemcitabine. Eleven trials obtained compared gemcitabine with combined treatment regimens that all included gemcitabine in the comparison arm and none of these trials detected any significant difference in one-year survival between the treatment arms. A single trial compared gemcitabine alone against a combination of 5-fluorouracil, leucovorin calcium, epirubicin, and carboplatin and no difference in one-year survival was detected between the treatment arms. Another single trial obtained compared gemcitabine plus concurrent radiotherapy with 5-fluorouracil plus concurrent radiotherapy and no difference in one-year survival between the treatment arms was detected.

- Pooling the one-year mortality data from the trials with one-year survival data available did not detect any overall statistically significant difference between the groups for gemcitabine alone versus another single-agent (relative risk [RR]=0.89; 95%CI, 0.79, 1.02; p=0.09), gemcitabine alone versus gemcitabine plus another single agent (RR=1.04; 95%CI, 1.00, 1.09; p=0.05), gemcitabine alone versus other combined treatment not containing gemcitabine (RR=1.22 (95%CI, 0.99, 1.51; p=0.06), or combined gemcitabine treatment versus other combined treatment not containing gemcitabine (RR=0.65 (96%CI, 0.94, 1.08; p=0.83).

POTENTIAL HARMS

The most common grade 3/4 (World Health Organization [WHO] or National Cancer institute-Common Toxicity Criteria [NCI-CTC] scale) adverse effects experienced with the administration of gemcitabine were neutropenia, anemia, leukopenia, thrombocytopenia, diarrhea, nausea, vomiting, and mucositis. One trial reported grade 3/4 anorexia.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Not Stated

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 May 22 (revised 2005 Jun 24)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Gastrointestinal Cancer Disease Site Group disclosed potential conflict of interest information.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Use of gemcitabine in the treatment of advanced pancreatic adenocarcinoma. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2005 Jun 24. Various p. (Practice guideline; no. 2-10). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. This NGC summary was updated by ECRI on December 17, 2001 and most recently on June 23, 2003. The most recently updated information was verified by the guideline developer as of July 16, 2003. This summary was updated again on April 19, 2004. The information was verified by the guideline developer on April 29, 2004. This NGC summary was updated on August 18, 2006. The updated information was verified by the guideline developer on August 23, 2006.

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